Don't stress about it!

Is stress management a disease-modifying therapy for multiple sclerosis?

Christoph Heesen, MD
Stefan M. Gold, PhD

Correspondence & reprint requests to Dr. Heesen: heesen@uke.uni-hamburg.de

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Psychological stress has been suspected to play a role in multiple sclerosis (MS) since Jean-Martin Charcot first described the disease.[1] Moreover, patients with MS intuitively make a connection between times of high psychological stress and exacerbations of their illness.[2] In contrast to this anecdotal evidence, a systematic review by a task force assembled by the American Academy of Neurology in 1999 concluded that "at present, the prospective data are insufficient to establish any such relationship [between psychological stress and MS] with reasonable medical certainty."[3]

Since then, however, numerous prospective clinical studies have supported a link between high stress and disease exacerbations,[4] including studies using objective MRI criteria for disease activity.[5] The most dramatic example was provided by a study demonstrating that exposure to potential missile attack during a 6-week period of hostilities increased the relapse risk in a cohort of patients with MS in Northern Israel by approximately 3-fold.[6] Intriguingly, a very similar finding was reported in a cohort of patients with MS in Lebanon during the same 6 weeks.[7] While these clinical studies clearly support the plausibility of the hypothesized association between psychological stress and MS exacerbations, observational studies have methodologic and conceptual problems that are difficult to overcome. For example, beginning inflammatory activity itself could be responsible for changes in stress perception, thereby reversing the cause-effect relationship. In addition, large interindividual differences in what is perceived as stressful, and the buffering effects of coping styles, make psychological stress notoriously difficult to measure. Thus, as is the case with any risk factor, only intervention studies are suitable to determine a causal role of stress or stress reduction in modifying MS disease activity.

In this issue of *Neurology*®, Mohr and colleagues[8] present results from the first such trial with exactly this aim: to reduce psychological stress with a behavioral stress management intervention and to evaluate the effects on disease activity with a widely accepted, objective MRI marker typically used in proof-of-concept studies of novel pharmacologic compounds.

Their treatment consisted of a 24-week stress management oriented behavioral intervention with 50-minute face-to-face sessions each week, compared to a wait-list control group in a cohort with clinical or MRI-documented disease activity. In the intervention group, patients developed fewer new lesions and a higher percentage of patients remained lesion-free (both Gd+ lesions as well as new T2 lesions) compared to patients in the control group. Generally, these findings appear to support the hypothesis of an anti-inflammatory effect of the intervention. In addition, self-report data suggest that levels of perceived stress declined substantially in the intervention group but not the control group. Together, these data indicate that behavioral stress reduction may help to prevent the occurrence of new brain lesions in MS. In this respect, the study may represent the first direct evidence for a causal link between stress and inflammatory activity in these patients.

However, the treatment effects surprisingly disappeared almost immediately after the end of the intervention. This is somewhat puzzling since the explicit goal of the intervention was to teach "problem solving skills, relaxation, increasing positive activities, cognitive restructuring, and enhancement of social support." If the participants learned and implemented these new skills during the trial, and this is what was responsible for decreased inflammatory activity during the intervention, why then were they not able to maintain this afterwards? One possibility would be that maintenance of these behaviors requires continuing active support as provided in the intervention setting. A nonmutually exclusive explanation for the lack of sustainable effects is the possibility that a nonspecific component of the intervention, such as providing social support, may be the active component of the counseling sessions.

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From the Institute for Neuroimmunology and Clinical MS Research and Department of Neurology, University Medical Center Eppendorf, Hamburg, Germany.

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What does this trial tell us about the relationship between stress and disease activity in MS? The good news is that the intervention apparently did something that was beneficial with regard to prevention of lesion formation on MRI, although it remains to be elucidated what exactly the beneficial component of the intervention was. Whatever the active component turns out to be, however, it is likely to be psychological in nature. The bad news is that even the enormous effort of the intervention with weekly face-to-face sessions for 24 weeks showed no sustained effects. Furthermore, two-thirds of eligible patients declined to participate, casting some doubts on the applicability of such interventions to the general MS population.

Taken together, the study provides class I evidence for an anti-inflammatory effect of weekly meetings with a psychologist over 24 weeks. It adds to the emerging class I evidence of novel behavioral interventions for MS in areas where current drug treatments show only weak or no effects. For example, cognitive behavioral fatigue management[9] as well as mindfulness training[10] lead to substantial and sustained effects on fatigue and depression.

Although often self-evident in daily routine, scientific work in a biopsychosocial model of disease is still scarce. Conversely, the evidence for the relevance of experiences, expectations, and behavior on brain functioning is growing.[11] Clinical research should make more use of it.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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